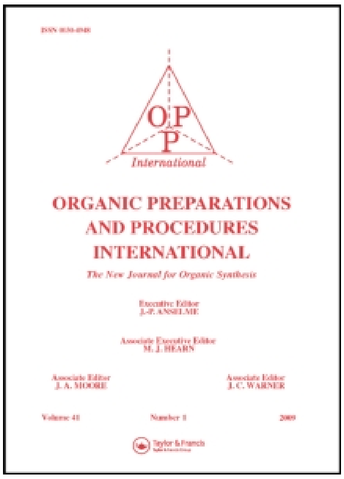

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THE SYNTHESIS OF 4,7-DIHYDRO-1,3-DITHIEPIN

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THE SYNTHESIS OF 4,7-DIHYDRO-1,3-DITHIEPIN[1]

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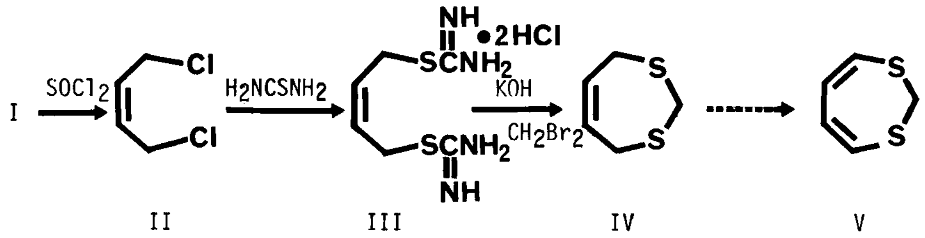
As part of a synthetic program directed toward the synthesis of polycyclic sulfur compounds, we required an efficient, large-scale preparation of diene V. As V has been shown to give a Diels-Alder adduct with N-phenylmaleimide,[2] reaction with other dienophiles would provide access to a variety of this class of derivatives. A procedure for the transformation IV → V is available,[2a] but only a brief reference is made to the synthesis of IV without experimental details or physical properties.[2a,3]



We now report, in complete detail, the synthesis of 4,7-dihydro-1,3-dithiepin (IV) from cis-2-butene-1,4-diol (I) in an overall yield of ca. 40%. The procedure is particularly convenient since it allows a large scale preparation of the bis-isothiuronium salt (III), which on formation, crystallized analytically pure and in excellent yield. The heat liberated during this crystallization is surprisingly high and due care must be exercised (cf. Experimental). Best results were obtained when cis-1,4-

dichloro-2-butene (II), freshly prepared from I was used.

EXPERIMENTAL[4]

cis-1,4-Dichloro-2-butene (II). - Thionyl chloride (1,640 g, 13.8 mol) in chloroform (1.5 ℓ) was added dropwise over a period of 6 hrs to a stirred mixture of diol I[5a] (528 g, 6.0 mol) and triethylamine (10 ml) in chloroform (750 ml), cooled in an ice-water bath. After the addition was complete, the dark green mixture was then refluxed overnight. Chloroform and excess thionyl chloride were removed by fractional distillation at atmospheric pressure[5b] and the residue was distilled under reduced pressure to yield cis-1,4-dichloro-2-butene (631 g, 84%),[5c] bp 50-60°/ 12 mm,[6] lit.[7] 55-60°/12 mm.

Bis-isothiuronium salt (III). - A 3-necked, 5-ℓ flask with a mechanical stirrer was charged with II (563 g, 4.5 mol), thiourea (752 g, 9.9 mol) and 95% ethanol (2 ℓ). The two remaining necks were each fitted with two 30 cm condensers in series. The reaction was initiated by heating to 40°. After removal of the heat source the reaction became highly exothermic. Under these conditions the solvent refluxed, and the thiourea went into solution. Almost immediately, the isothiuronium salt crystallized with great evolution of heat. The thick slurry was heated gently under reflux overnight. Filtration of the product, subsequent washing with 95% ethanol, and drying (25°/0.5 mm) yielded III (1,040 g, 83%);[8a] mp crude 197-200° (dec.), recrystallized from 95% ethanol, 199-201° (dec.); nmr (D_2O, DSS) 4.0 (4H, d), 6.0 (8H, S), 5.9 (2H, t); ms: m/e; 129(7), 86(70), 85(67), 76(59), 60(20), 43(100), 42(32), 38(27), 28(18).

Anal. Calcd. for $C_6H_{14}N_4Cl_2S_2$: C, 26.00; H, 5.09; N, 20.21;
Found: C, 25.87; H, 4.98; N, 20.27.
(crude) Found: C, 25.93; H, 5.00; N, 20.22.

4,7-Dihydro-1,3-dithiepin (IV). - To a mechanically-stirred slurry of the isothiuronium salt, III (277 g, 1.0 mol) in methanol (3 ℓ) was added portionwise at 0° over 1 hr, potassium hydroxide (330 g, 5.0 mol/85% pure). The mixture was allowed to reach ambient temperature and stirred for 16 hrs. To this, dibromomethane (218 g, 1.25 mol) in methanol (1 ℓ) was added dropwise over a period of 6 hrs at 0° and left to warm slowly to room temperature overnight. Stirring was continued for an additional 60 hrs or until the reaction mixture did not cause lead acetate paper to become yellow (thiolate ion still present). The reaction mixture was then filtered to remove the salts and polymer, and the filtrate concentrated by flash evaporation to about 700 ml of residue (some solid present), which was transferred to a 2-ℓ separatory funnel containing ether (1.2 ℓ). The mixture was washed with water (3 x 300 ml) until the aqueous layer was clear. The ethereal layer was then dried ($MgSO_4$) and flash evaporated to yield IV (69 g, 52%)[8b] as a light-yellow crystalline solid, mp 38-42°. Recrystallization from pentane or sublimation (40°/12 mm) yielded an analytically pure sample, mp 51-52° which showed signs of decomposition (mp 46-51°) after two months in a closed vial. Substitution of diiodomethane for dibromomethane consistently gave slightly higher yields (ca. 60%). However the insoluble sticky polymer formed during the reaction tended to interfere with the mechanical stirring. Nmr ($CDCl_3$, TMS) 3.4 (4H, 2d), 4.0 (2H, S), 6.0 (2H, m); ir (cm^{-1}) 3010, 2950, 2890, 1630, 1420 (S), 1325, 1250, 1225, 1205 (S), 1145 (S), 1135, 880, 795 (S), 760 (S), 735 (S), 695, and 660; ms: m/e; 132(94), 86(55), 84(42), 78(100), 71(20), 67(23), 52(11), 50(22).

Anal. Calcd. for $C_5H_8S_2$: C, 45.41; H, 6.10;
Found: C, 45.25; H, 6.48.

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4. Infrared spectra were recorded on a Perkin-Elmer Model 257, grating spectrophotometer, calibrated against the 1602 cm^{-1} of polystyrene; ^{1}H-nmr spectra on a Varian T-60. Chemical shifts are recorded in ppm (δ), from TMS or DSS, and the following abbreviations used: S, singlet, d, doublet, t, triplet, m, multiplet. Mass spectra were determined with a Produkter AB LKB 9000 mass spectrometer using a direct probe insertion, heating at 40°. The 8 most intense peaks are listed with the percentages in brackets. Melting points were obtained using a Gallenkamp block apparatus and are uncorrected. Glc data were gathered on an F & M model 5751 Research Chromatograph. Microanalyses were performed by Dr. C. Daesslé of Montreal or by Midwest Microlab, Inc., Indianapolis, Indiana.

5. a) Obtained from Aldrich Chem. Co. as 91% *cis*; b) Removal of $CHCl_3$ at reduced pressure led to lower yields; c) Distillation was discontinued when a greenish substance began to distill.

6. Glc analysis, using 20% carbowax 20M on 60/80 mesh acid washed/DMCS Chromasorb W, 12' x 1/8", flow rate 50 ml/min programed from 100-200° at 20°/min held at 200°, showed the compound to be free of its *trans* isomer. Retention times, *cis*, 5.4 min; *trans*, 5.8 min.

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8. a) Yields ranged from 80-85%; b) Yields ranged from 50-55%.

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